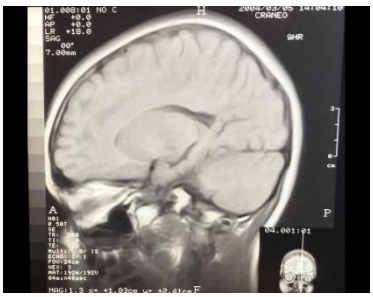

LOCAL AND DISTANT FUNCTIONAL CONNECTIVITY PATTERNS IN ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

FINAL DEGREE PROJECT

Biomedical Engineering

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ABSTRACT

Attention Deficit Hyperactivity Disorder (ADHD) is said to be one of the most controversial and common neurodevelopmental Brain disorders. However, there is no potential diagnostic biomarker found yet. Recently, the neuroimaging group have conducted a cross-sectional study in which by using graph theory approach, local and distant functional connectivity patterns were compared between ADHD and Normal Developing (ND) children. They found that children with ADHD manifest increased local connectivity in multiple brain regions. Results suggested an immature functional state in some brain networks and were in line with the view of ADHD as a disorder in accordance to the maturational deviation model. The main goal of present study is to depict the functional maturational level of the Brain in adults with ADHD based on local and distant connectivity by comparing cross-sectionally ADHD and control samples. Results found are consistent with a decrease in local Functional Connectivity (FC) in multiple brain networks, which is translated into reduced integration. Moreover, a negative correlation between symptom severity and FC has been found within main nodes of a specific network supporting the lack of integration in it.

INDEX OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATONS

(ADHD)-Attention Deficit Hyperactivity Disorder

(FC) – Functional Connectivity

(DM) – Default Mode

(DA) – Dorsal Attentional

(VA) – Ventral Attentional

(FP) – Frontoparietal

(DMN) – Default Mode Network

(DAN) – Dorsal Attentional Network

(VAN) – Ventral Attentional Network

(DSM) – Diagnostic and Statistical Manual of Mental disorders

(NA) – Noradrenaline

(MR) – Magnetic Resonance

(NMR) – Nuclear Magnetic Resonance

(MRI) – Magnetic Resonance Imaging

(fMRI) – functional Magnetic Resonance Imaging

(rs-fMRI) – resting state functional Magnetic Resonance Imaging

(BOLD) – Blood Oxygen Level Dependent

(M) – Magnetization

(Bo) – Strong Magnetic Field

(B1) – Radio frequency field

(RF) – Radio Frequency

(EPI) – Echo Planar Imaging

(DTI) – Diffusion Tensor Imaging

1. INTRODUCTION

1.1. Motivation

Attention Deficit Hyperactivity Disorder (ADHD) is considered one of the most common neurodevelopmental disorders. Core symptoms include inappropriate levels of inattention, hyperactivity and impulsivity, being the most frequent and investigated ADHD phenotype the one with predominance of inattention [1]. Such symptoms manifest during pre-school and in some cases prevail during adulthood affecting not only the academic and vocational performance but also the social adaptations [2-4].

The human brain can be conceptualized as a complex organized network, in which billions of neurons are interconnected forming functional areas (Jonathan D Power et al., 2010)[5] that interact to support cognitive functions [6]. Across development, a tendency has been found toward segregation between local anatomical regions and integration between selected distant ones in space [6]. In accordance to the maturational lag hypothesis, ADHD is said to involve a lag in brain maturation [7]. To support this, multiple resting state functional Magnetic Resonance Imaging (rs-fMRI) studies have been conducted. However, there are still studies pointing out that in ADHD brain trajectories reflect deviations from normal patterns [8] especially in terms of functional connectivity in some large-scale functional networks such as the attentional or the default mode (DM) [9-12].

During normal development, the Functional Connectivity (FC) of the brain goes *from a local to a more distant distribution* [13, 14]. Graph theory analyses, which include local and distant FC profiles; are considered a promising approach to studying brain networks [15-17].

1.2. Objectives and hypothesis

1.2.1. Objectives

The main goal of this study is to disentangle whether immaturity traits observed in children with ADHD persist into adulthood. For that purpose, local and distant functional connectivity patterns will be cross-sectionally compared between adults with ADHD and controls.

1.2.2. Hypothesis

Based on the previous study in children we expect to still find immaturity traits in the form of altered functional connectivity patterns that do not necessarily catch up with age. Moreover, we presume a relation between ADHD clinical symptoms severity.

1.3. Socioeconomic impact

Mental Illness has a global repercussion in society that not only affects the individual that suffers it in terms of employment, physical health or education but also to its surrounding environment, in which personal relationships or doctors are included. Although many effective mental health interventions are available, people often do not look for the attention they need. In fact, in 2011, only 59.96% of individuals with a mental illness have reported to receive treatment [18].

For the case of ADHD there is no reliable method of diagnosis established yet and it is the professional who has to gather information from multiple sources in order to make the diagnosis, sometimes leading to over-diagnosis. In fact, it was reported that just in America 6.4 million children have been diagnosed with ADHD [19]. Moreover,

treatments that indeed are expensive have been proved not to cure the patient, only improve/control some of the symptoms.

In terms of money, as already mentioned medication and treatment are costly. In fact, in 2007 a study reported that the 'cost of illness' for a person suffering from ADHD was around $14,576 [19]. For that reason, neuroimaging studies are being conducted in order to understand better this neurodevelopmental disorder and to find a potential diagnostic marker for ADHD.

1.4. Budget

Part of the present project's funding comes from COFUND M + VISION (from 2013 to 2016 research scholarship). Estimation for the expenses of the project is outlined in table 1.

TABLE I
BUDGET

	Number	Cost	Total (€)
Image acquisition	53 subjects	400 € per scan	21,200
Processing and storage of MRI scans	53 subjects	120 € per scan	6,360
Personal	4 person per month (PPM)	3,000 € per PPM	12,000
Other goods and services	-	-	10,000
Direct costs	-	-	49,560
Indirect costs (21%)	-	-	10,408
Total Costs	-	-	59,698

Table 1: Estimated project budget.

1.5. Regulatory framework

The study was approved by the Hospital de Vall d'Hebron Ethics committee. Signed consent was obtained after a detailed explanation of the study, from all participants. Subjects satisfied all the MRI safety requirements and the obtained images were anonymized in order to meet the Data Protection Act [20].

1.6. Outlines

The content of this work is organized in three main sections. First, we review basic concepts related to neurobiology of ADHD and MRI, together with structural and functional neuroimaging studies of the disorder. In the second section, we revise the implemented methodology (study design and participants, image acquisition and processing, functional connectivity and statistical analyses). Finally, we provide results obtained and discuss them, also pointing out both the potential limitations and future lines of research.

2. STATE OF THE ART

2.1. ADHD

According to the National Institute of Mental Health, ADHD is a brain disorder marked by an ongoing pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development. This neurobiological disorder [21] is characterized by three core symptoms known as inattention, hyperactivity and impulsivity. According to the Diagnostic and Statistical Manual of Mental disorders (DSM-IV) [22], ADHD can be divided into inattentive, hyperactive/impulsive and combined subtypes [23].

The symptoms for ADHD people associated with hyperactive and impulsive behavior most commonly arise between 3 and 6 years of age. For the inattentive ADHD subtype symptoms tend to appear in middle or later childhood. Thus, it has been suggested that the disorder is believed to be of childhood onset. With respect to the prevalence, ADHD occurs in approximately 5% to 7% of children and at 3.4% in adults [24]. Moreover, it has been proven that both environmental and genetic factors alter the neurological basis of the disorder [25].

2.2. History of ADHD

The ADHD concept has been evolving over the last two centuries. In 1978, a Scottish physician named Alexander Crichton was the first to describe a condition similar to what is known today as ADHD, but naming it '*Mental Restlessness* '. The two characteristics that prevailed were restlessness and the inability to attend to something during enough time and with perseverance in the accomplishment of tasks [26]. In 1845 the psychiatrist Heinrich Hoffmann did a piece of work where he described a dispersive, hyperactive and

impulsive behavioral pattern in children. This led to think that he must have treated and observed young people with similar behaviors [26]. In 1902 George Still published an article describing a developmental standard of 43 children whose features among others were lack of attention or low voluntary control to inhibit immediate gratification search. Moreover, he observed that behavior was not linked to rearing pattern. He defined it as '*Moral control defect* '[26].

At the end of the First World War, an epidemic lethargic encephalitis started in Europe. Initially, excessive levels of hyperactivity, impulsivity and inattention were associated to the disease, but when some people who were not suffering from such encephalitis exhibited the same 3 symptoms, a different explanation became necessary. They proposed that it was due to a minimal brain injury later called minimal cerebral dysfunction. Although this concept persisted during the following years, it progressively lost popularity [26].

It was in 1932, that doctors Franz Kramer and Hans Pollnow proved in parallel that hyperkinetic children did not present the observed physical manifestations in post-encephalitic cases [27]. They considered this as C*hildhood Hyperkinesis*. In the 50's, hyperactivity was considered as the core symptom while inattention passes to a second plane. This led to the *Hyperkinetic Syndrome* concept which initiated the definitive separation from 'Minimal Cerebral dysfunction'. At the beginning of the 60's Stella Chess used the term '*Hyperactive child syndrome*' with which she questioned whether the mood of children was innate or was dependent on the external context. It was not until 1992 that the OMS published the CIE-10 where it recognized ADHD as a clinical entity and included it in the disorders of behavior and emotions of onset in childhood and adolescence, a subgroup of hyperkinetic disorders [26].

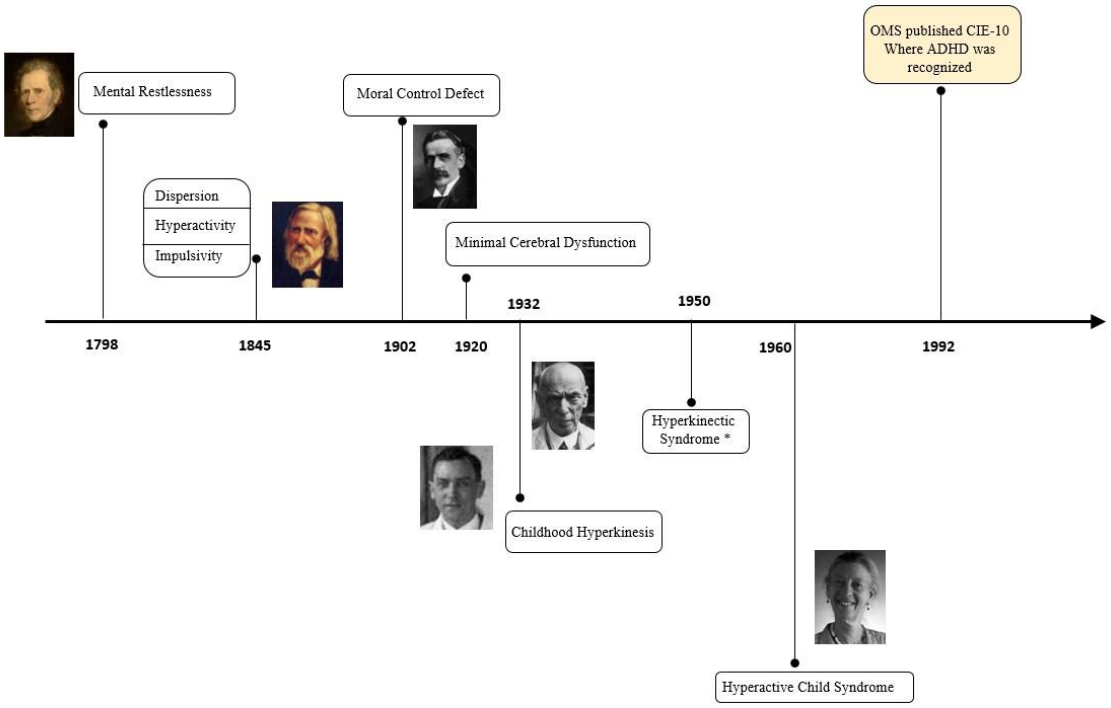

Figure 1: Timeline collecting the origin of the term ADHD. It goes from 1798 to1992, when it is recognized by first time.

2.3. Neurobiology of ADHD

During the last decade the neurobiological factor of ADHD has been in the crosshairs [25]. Multiple studies support the relationship between ADHD and possible neurotransmitter maladjustment or functional and structural alterations in brain regions [28-38]. In particular, it has been suggested that people with ADHD have variations on the transporter genes for glutamate, noradrenaline (NA) and dopamine neurotransmitters [39].

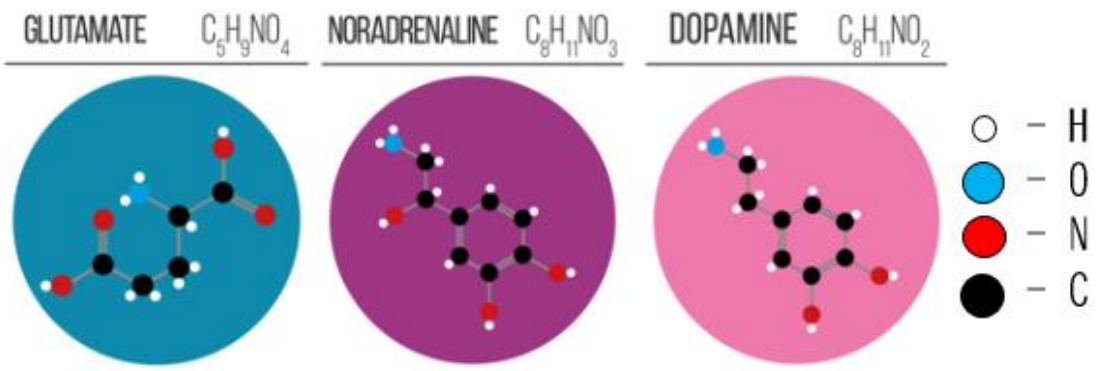

Figure 2: Chemical composition of the neurotransmitters glutamate, NA and dopamine [40].

According to [41], ADHD was the first disorder found to be the result of a deficiency of norepinephrine (also known as NA). High levels of it contribute to aggression, anxiety or hyperactivity while low levels are associated with a decrease in energy, motivation, focus, memory and mood [42]. With respect to dopamine it has been proved to be involved in the regulation of mood, memory, attention, learning and motor control. Low dopamine release has been related to reduced motivation and inattention. Moreover, such low levels can result in impaired motor control. On the contrary, high levels may result in aggression, hyperactivity and Tourette's syndrome [42]. Finally, glutamate is known for being implicated in many brain functions such as cognition, learning and memory. Despite few studies having been made to analyze the role of glutamate in ADHD, it has been reported that low concentrations of it in the basal ganglia (which includes the Caudate and Striatum) are associated with more severe symptoms of inattention [43].

2.4. MRI Background

Actually, the Magnetic Resonance (MR) technique can be considered as one of the most important medical imaging modalities. This is due to its versatility and non-invasive properties (i.e. its capacity for being free of hazards related to ionization when generating thin sections). Moreover, the time of acquisition is relatively short and both the direction and angle from which an image is obtained are flexible [44, 45]. Therefore, these and the

high contrast resolution and multi-planar capacity are some of the advantages that make this modality so attractive and useful [45].

2.4.1. Introduction

MR allows for visualization of both structural and functional information related to the human body. This technique is based on the physical phenomenon known as Nuclear Magnetic Resonance (NMR).

It was in 1938 when NMR was described and measured in molecular beams for the first time [46]. In 1946 Felix Bloch and Edward Purcell proved independently the NMR phenomenon in liquids and solids, which indeed laid to the physics of MRI. In 1952 they shared the Nobel Prize. In this year, also the first NMR unit was created thanks to Russell H. Varian who in 1951 filed the "Method and means for correlating nuclear properties of atoms and magnetic fields". Moreover, it was Erwin Hahn in 1951 and 1952, who developed the spin echo method and the Free Induction Decay (FID), respectively and in 1966 Richard R Ernst developed Fourier transform NMR spectroscopy. In 1971 Raymond Damadian conducted a NMR experiment where rat tumors were analyzed by measuring T1 and T2 relaxation times. Later on, Peter Mansfield and Paul Lauterbury published the first NMR image. It is in 1977 when the first MRI body scan of a human being is done [47, 48].

The phenomenon of magnetism has its origin in the movement of electrically-charged particles [49]. Nuclei with an odd number of protons, neutrons or both share a spin (i.e. an entirely quantum-mechanical property that is associated with an intrinsic angular momentum) and precession [50].

When the human body is introduced in a strong magnetic field (Bo), positively-charged hydrogen protons (the human body is comprised of cells that contain water molecules which indeed are principally made of these atoms) interact with it, resulting in the body Magnetization (M), where protons align with the field (the spins tend to sort themselves into orientations either generally aligned with or opposed to Bo leading to two spin states, parallel and anti-parallel) and precess at a specific rate known as Larmor frequency [50-53]. This frequency, also named precession frequency is proportional to the strength of

Bo and the gyromagnetic constant (γ) (i.e. specific particle ratio that includes size, mass and spin as intrinsic properties) [54]. In terms of quantum mechanics, the explanation that lies behind Larmor frequency is given by the relation between Planck's equation and Zeeman Effect (i.e. both states are physically separated reflecting a difference in energy). The protons' magnetic moment (μ) will tend to align with Bo and experience a twisting force, also known as torque (τ). In terms of energy, when no τ is experienced μ will be in its lowest energy state and aligned parallel to the field. On the contrary, when aligned antiparallel μ will be in its highest energy state because extra energy would be required to move and maintain it in this position.

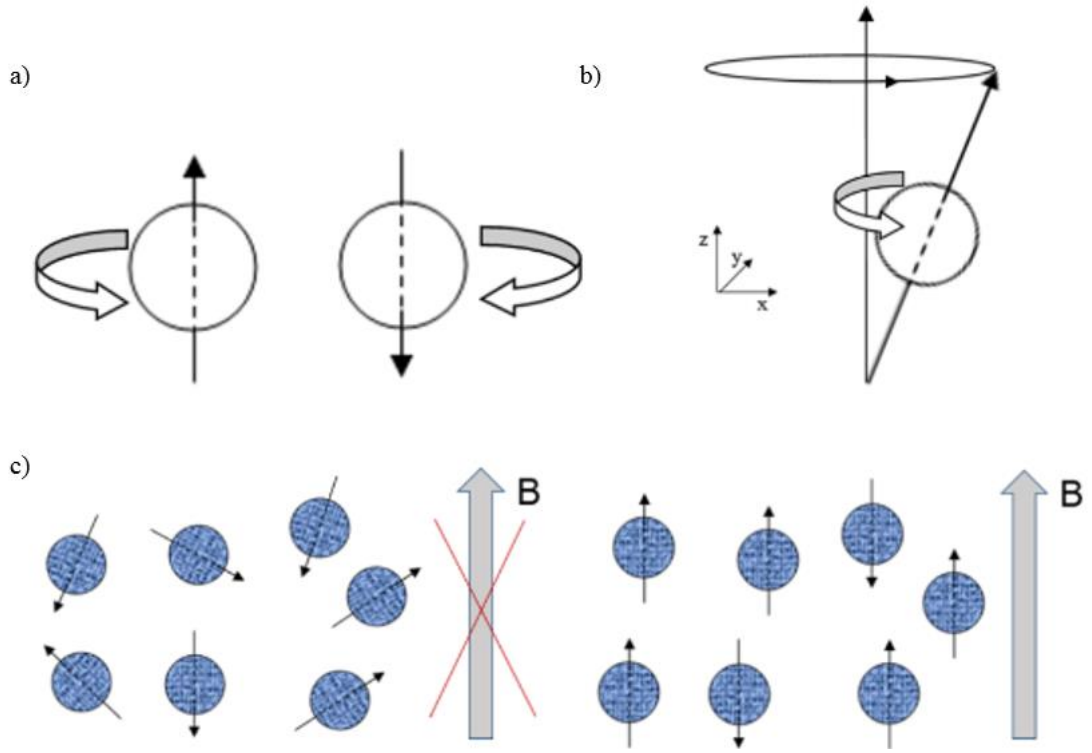

Figure 3: Schematic representation of a) antiparallel and parallel spin alignment, b) an antiparallel spin precessing and c) proton alignment in the presence of Bo.

When a perpendicular radio-frequency field (B1) near the Larmor frequency is applied to Bo, the tip of M away from its initial alignment with Bo will occur, resulting in M leaving its equilibrium state and performing a simple rotation. This process is known as excitation. Since M is a rotating vector in space it can be decomposed into three components, each as a function of time— $M_X(t)$ *and* $M_y(t)$ *known as transverse components* and $M_z(t)$ *known as the longitudinal component.* When B1 is applied only

during a small period of time it is known as a RF pulse. After a pulse is applied, signal decay occurs because the individual spins that comprise M interact with each other and their environment, resulting in M to return to its thermal equilibrium state in which M is a constant magnitude (Mo) and parallel to Bo. During this process known as relaxation, energy is released in the environment by the spin system. This realignment generates the RF signal that will be detected by the MRI imaging system which will give the MR image (i.e. a map of the distribution of the MR signal) [55]. In order to describe how the reestablishment of thermal equilibrium of M after the generation of the signal takes place T1 and T2 time relaxation constants are used. T1 relaxation, also known as spin-lattice relaxation is related to the energy transfer from a nuclear spin system to its environment (it is called the lattice, because this process was initially observed in crystals). T1 is the time constant for regrowth of longitudinal magnetization (M_z). It only appears when a proton encounters an oscillating B1 at the Larmor frequency. This transfer of energy to the lattice causes a slight rise in temperature. T2 relaxation, also known as spin-spin relaxation is related to how nuclear spins interact on each other. During this process, transverse components of magnetization (M_X and M_y) decay or lose their phase coherence (spins no longer precess all together) resulting in a reduction of the overall M. T2 is the time constant for this decay or dephasing of M_X and M_y [54, [56, 57].

Therefore, T1 signal is related to the speed of realignment with the magnetic field –the quicker the protons realign, the greater T1 signal. With respect to T2 signal, it relates the speed of proton spin dephasing –the slower the dephasing, the greater the T2 signal [58]. However, certain MR sequences that use gradient echoes and relatively long echo time (TE) values are called T2*-weighted. T2*can be considered as an "observed" or "effective" T2. T2*-sensitive sequences also form the basis for functional MRI (fMRI) using the Blood Oxygenation Level Dependent (BOLD) technique [58]. Additionally, when MR slices are acquired in a frame period between 50 and 100 ms they receive the name of Echo-Planar Imaging (EPI) [59]. This technique, due to its short acquisition time and increased temporal resolution is allowed to measure brain activity.

2.4.2. Functional MRI

fMRI, also known as BOLD imaging is referred as the imaging of brain activation, which varies according to blood flow changes in cerebral regions [60]. During this process, oxygen is delivered to neurons by hemoglobin in capillary red blood cells. When neuronal activity increases there is an increased demand of oxygen and the local response is an increase in blood flow to regions of increased neural activity. Hemoglobin is diamagnetic when oxygenated (oxyhemoglobin) but paramagnetic when deoxygenated (deoxyhemoglobin). The local ratio between such magnetic properties is what leads to small differences in the MR signal of blood depending on the degree of oxygenation [61].

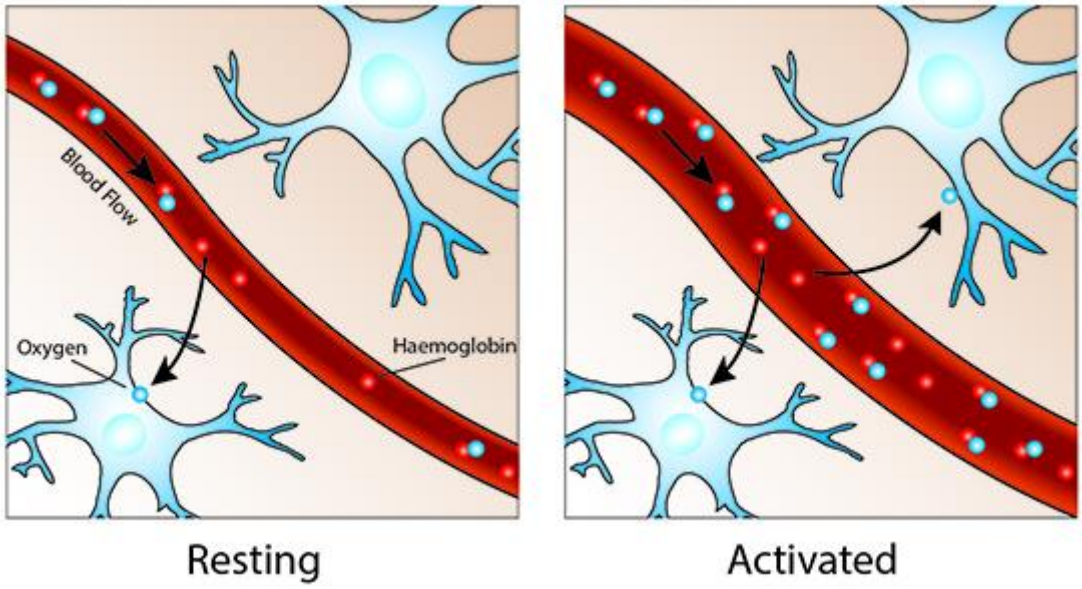

Figure 4: It can be seen how during increased neuronal activity, blood flow in regions where there is high demand in oxygen increases too [61].

In a typical task BOLD-fMRI experiment the subject is asked to intermittently perform a task (such as finger tapping or silent word generation) while lying in the scanner. Brain images are obtained at rest and during task performance. Then, a statistical comparison between task and rest allows generation of activation maps that can be overlaid on anatomical images. The 'activity' in a voxel during a task is defined as how closely the time-course of the signal from that voxel matches the expected time-course obtained from the convolution of the Hemodynamic Response Function (HRF) (i.e. blood delivery/ vascular response to active neural tissue) [62] and the task vector. Voxels whose signal

corresponds tightly are given a high activation score, voxels showing no correlation have a low score and voxels showing an opposite pattern of activation (deactivation during the task) are given a negative score. These can then be translated into activation maps [61].

A relatively new and popular fMRI method consists in scanning the participants while they stay still. This method is known as resting state fMRI (rs-fMRI), and it is used to measure spontaneous brain activity through spontaneous BOLD signal fluctuations [61]. According to Hebbian Theory, "cells that fire together wire together" [63] and, therefore, the regions of the brain that show similar activity during rest tend to be active during similar tasks [64, 65]. This coactivation level is what we call FC and its organization in the brain forms the functional networks, which have been shown to be related to with the different cognitive processes [66].

One of the most widely described networks is the Default Mode Network (DMN) (i.e. a network that show low levels of activity when engaged in any specific task [67]), which is related to high order cognitive functions as the Theory of Mind and has been found impaired in several disorders [68]. Taking altogether, rs-fMRI is considered as a potential tool to understand brain functioning from a systems biology perspective [69] and, moreover, as a way to find biomarkers for multiple neurological and psychiatric diseases [70, 71].

2.5. Graph theory and networks

The human brain is probably the most complex container of interconnected networks in nature [72]. Graph theory and Network science applications have helped in understanding how neuronal network structure is linked to human cognitive functions, contributing to both map the brain from structure to function and to understand age-related brain functioning and dysfunction [72-74]. Network-based algorithms help to define how the brain is organized and its alterations at different levels [72, 74].

Graph theory brain network is defined as the representation of brain architecture consisting of links (i.e. functional or anatomical connections) interposed between nodes (i.e. brain regions) [72, 75].

Many studies have reported that such neural networks share a small-world behavior (i.e. nodes of a network show high levels of local clustering among them and short paths that globally link all nodes of such network) which was originally described in social networks [76].

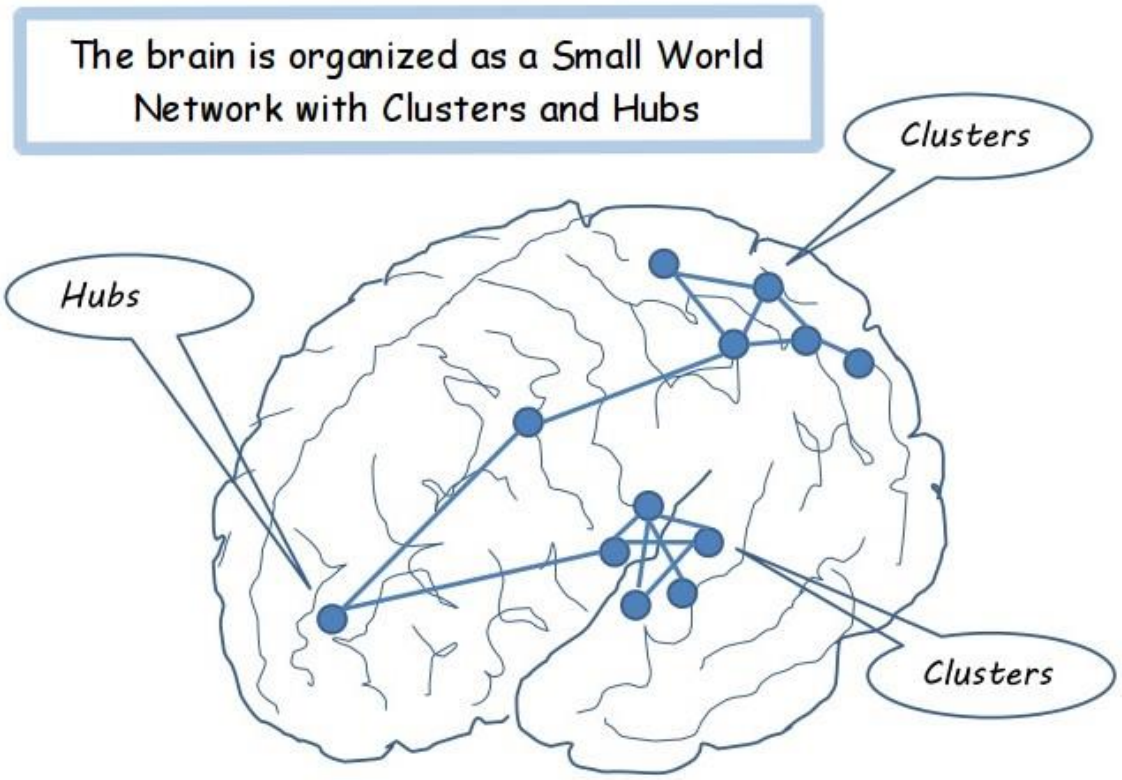

Figure 5: Graphical view of how nodes or hubs and clusters are represented and how they are linked between them [77].

From a mathematical point of view, a network is a matrix where columns represent how related is the current node (represented by rows) to every other node in the network. These links are used to estimate the strength of correlation or causal interactions in functional networks. If networks are binarized (i.e. unweighted) the links indicate if a connection is absent or present [72, 78].

However, there are some properties of brain networks that determine their maturation and level of effectiveness: segregation and integration [79]. The concept of segregation refers to the specialization of proximate regions for different tasks and, consequently, a differentiation of those regions' activity. Integration refers to the convergence of cerebral

functions, indicating that brain processes occur through a widely distributed structure in which different regions are implicated [79].

In terms of neurodevelopment, the maturation process of the brain is characterized by a segregation of proximate regions and an integration of distant regions, giving place to the functional networks. A notable exception to this pattern of development is the maturation of the visual network, which is comprised only by one broad region of the occipital cortex, so its integration is mostly local. For all this, the local and distant functional connectivity method is an indirect measure of the level of maturation of a brain through segregation and integration.

2.6. Neuroimaging ADHD studies

Brain imaging has been a breakthrough technology for cognitive neuroscience [80]. It was in 1970 when for the first time and thanks to the introduction of neuroimaging techniques that a brain image was obtained [81]. Neuroimaging techniques are used in both research and clinical practice in order to image the central nervous system [82]. ADHD has been investigated with brain scanning experiments more than any other childhood disorder [83] and thanks to them many important advances have been performed in the understanding of the neurobiology that underlies the clinical picture of this disorder.

2.6.1. Structural alterations in ADHD

From structural neuroimaging studies, structural alterations have been observed in children with ADHD mainly in basal ganglia, cerebellum, frontal lobes and parietal and temporal regions [84]. Moreover, evidence has been shown for a maturational delay in brain structure from longitudinal studies (i.e. studies where data is obtained from observing repeatedly same variables over a period of time) [85]. In adults with ADHD, a decrease in cortical thickness has been observed in posterior-anterior cingulate, temporo-

occipito-parietal junction and bilateral dorsolateral and orbitofrontal cortices [86]. With respect to the volume, while the nucleus accumbens showed an increase of it, the right anterior cingulate, left superior-dorsolateral prefrontal cortex and the overall cortical gray matter had a reduction in volume [87, 88].

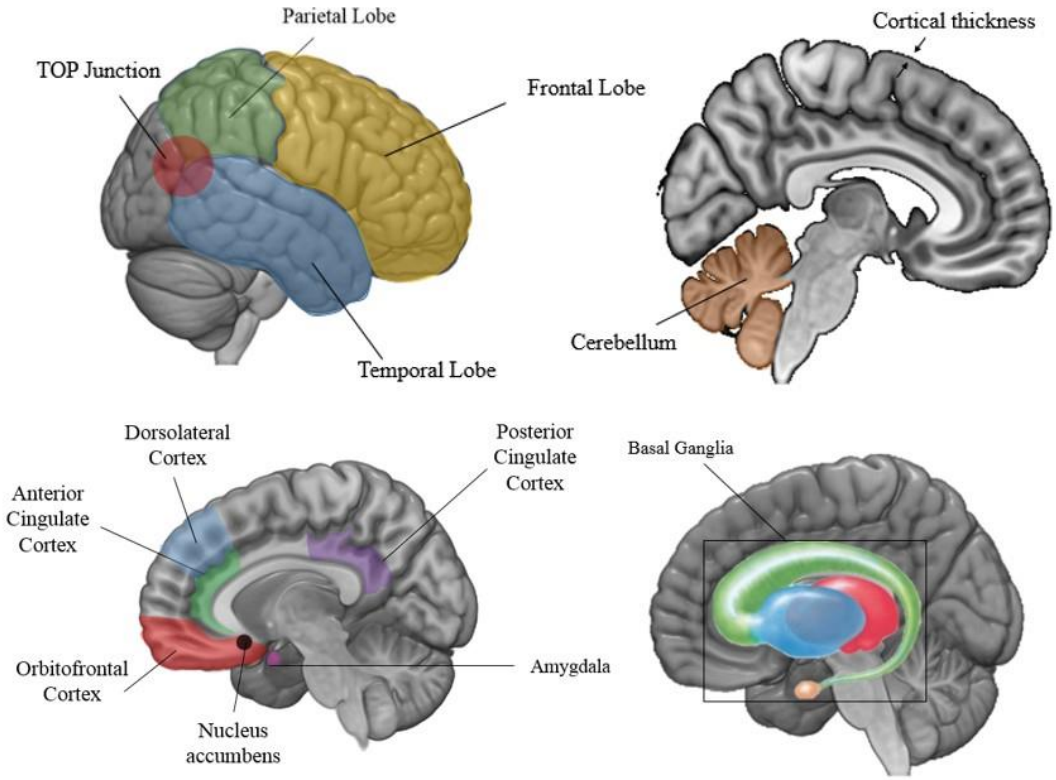

Figure 6: Visual representation of multiple anatomical regions where structural alterations in ADHD have been observed.

Moreover, alterations in white matter tracts' deficits were tested using the Diffusion Tensor Imaging (DTI) technique (i.e. an MRI technique image where the direction of the movement of water molecules is used as contrast). The results showed a reduction in size of the right-hemisphere fiber tracts in both the cingulum bundle (i.e. white matter fibers that project from the cingulate gyrus) connecting the dorsolateral prefrontal cortex with the anterior cingulate, and the longitudinal fascicle that is connecting the parietal and prefrontal regions, which in fact have been reported to be crucial for attention and executive functions, respectively [89].

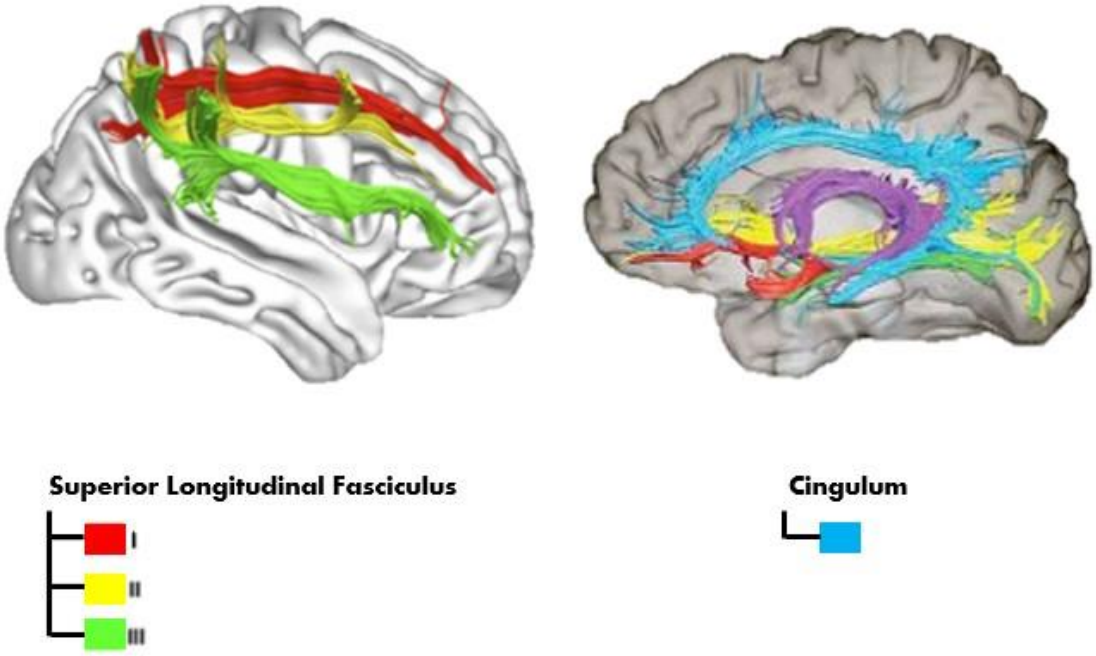

Figure 7: Representation of the three branches of the Superior Longitudinal Fasciculus according to *Thiebaut de Schotten et al. (2011) [90]* and the Cingulum bundle [89].

A recent cross-sectional mega analysis was conducted. The results revealed that volumes of the putamen, hippocampus, caudate, accumbens, amygdala and internal cranial volume were smaller in ADHD individuals. An exploratory lifespan model (i.e. a type of research used to obtain a first approach to the problem) suggested that both a delay of degeneration and maturation as effect sizes (i.e. a quantitative measure of the magnitude used to describe differences between two groups) were higher in most o children subgroups versus adults in the regions of the accumbens, putamen, amygdala and caudate while there were no difference for the thalamus or pallidum [92].

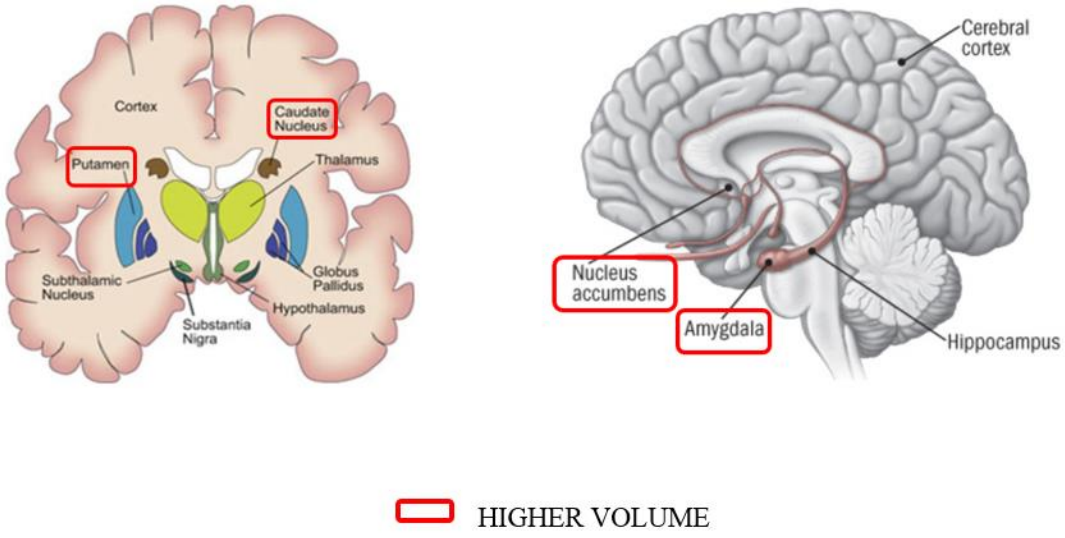

Figure 8: Visual representation of the main regions where volume was affected according to the cross-sectional mega analysis conducted by *Hoogman et al. (2017)* [93].

2.6.2. Functional alterations in ADHD

The functional imaging field has evolved rapidly over the past two decades, proving novel ways to examine questions regarding the pathophysiology of ADHD [94]. The first ADHD studies using fMRI focused on detecting regions with different levels of activation during certain tasks. However, the usage of rs-fMRI and the development of new statistical techniques are suggesting that ADHD involves a general alteration of the brain where all systems from perceptive to those related to high order cognitive functions are involved. Multiple connectivity studies focused on rs-fMRI have been used to analyze the brain network connectivity patterns and the temporal correlation of neural activity between different brain regions [11], making a distinction between those disconnected and connected in terms of function (i.e. positively temporally correlated) and, being the last ones a key in the detection of the components of different functional networks [11], [95].

Task positive networks include regions of increased activation in functional brain imaging studies during cognition tasks [96, 97]. The Ventral Attentional Network (VAN) is a key task positive network that traces the external stimuli's salience [97, 98, 100] and regulates switching between task negative (DMN) and task positive modes of cognition [101, 102]. Patients with ADHD exhibited greater within-network FC in VAN [103]. It

was also found decreased salience to Dorsal Attentional Network (DAN) FC in ADHD [103] and increased dorsal and ventral inter-network FC. Moreover in Kessler, Angstadt et al. 2014 [104], decreased network connectivity between somatomotor and DAN was found. They also reported decreased connectivity between frontoparietal and DA and VA networks and increased FC between the visual and DAN.

Moreover, increased within-network FC has been shown in the visual [104, 9] and affective/limbic networks [105]. In sensory networks more significant within-network FC [106] was found, and increased local efficiency with slightly decreased global efficiency in terms of small world brain functional network distribution in children with ADHD [107] was also reported.

In executive networks, an increase of FC during response inhibition tasks was found within the frontal network [108, 109] while a reduction in FFC was observed within the frontal-parietal-cerebellar executive control network [110, 104]. Moreover, a meta-analysis of functional studies was performed and showed that during inhibition tasks adults with ADHD present decreased activation within the frontal network [111].

The DMN instead is a network whose regions activate during rest and deactivate when performing tasks. In normal conditions it is, therefore, negatively connected with task positive networks even at rest [112]. At early stages this network is barely connected, but during adolescence its integration increases [113, 102] and it becomes segregated from task positive networks [114]. In both children and adults with ADHD the strength of this negative FC was decreased, pointing to a lack of segregation between these networks [115, 116], while within network connectivity was increased indicating a greater integration of DMN [133]. However, a lack of integration in the form of disconnection between the two main modules of the DMN was reported in ADHD [115].

In terms of neurodevelopment, increased integration in the visual and VAN, and increased segregation between both DA and VA networks and DA and visual networks contribute to a more mature brain. However, the increased integration in sensory networks and decreased segregation in the executive, DM and the rest of attentional networks suggest a less mature brain supporting the idea of abnormal brain development in ADHD. With respect to the integration of the DMN, further studies need to be conducted in order to determine how alterations within this network affect the brain in this disorder.

2.6.3. ADHD hypothesis

Based on the results obtained from research studies, two neurodevelopmental hypothesis appear to be relevant to ADHD. They are known as the developmental deviation model and the maturational lag model [118].

The neurodevelopmental model of developmental deviation which is also known as maturational deviance, suggests that ADHD brain is not approaching normality or complete maturation at any stage during the lifespan and proposes that ADHD is the result of abnormal functioning of the central nervous system [119]. The second neurodevelopmental hypothesis is the maturational lag model which suggests that ADHD is the result of a lag in the normal time for development. According to this hypothesis, the behavior of children with ADHD is abnormal with respect to their age [120]. Hence, it stipulates that despite an ADHD individual presenting delay in some aspects of its neurological maturation, at the end it will 'catch up'. It has been stated that the brain of ADHD children maturate, on average, about three years later with respect to children without ADHD, with 50% of their cortex only reaching maximum thickness around the age of 10. However, it has been said that from one cortical region to another the lags in maturation appear to differ. In other areas, such as the primary motor cortex of the ADHD brain show signs of being faster maturated than in brains without ADHD [120, 121].

There are multiple studies based on structural MRI that support the latter theory [122], [123]. However, recent studies based on rs-fMRI have shown that although the results obtained are in accordance with the delay of neurological maturation, they do not seem to achieve a 'catch-up' with age [14].

2.6.4. Diagnosis in ADHD

Diagnosis of children with ADHD is one of the most studied and controversial problems about the disorder [124]. Currently, there is no consensual clinical diagnostic model available. Moreover, neither neurobiological nor neuroimaging studies are available to establish this diagnosis with certainty [125]. In addition, despite multiple neuroimaging

studies having been conducted to find a diagnostic marker for ADHD [126] this has not yet been found.

Over-diagnosis could be accounted for by the diverse diagnostic methods. In the absence of such diagnostic markers, the methods used to evaluate are usually based on scales of assessment of people close to the subject [127]. In addition to this, other factors influencing prevalence (i.e. the proportion of a particular population found to be affected by a medical condition) are the type of sample chosen and sociodemographic characteristics [128-130]. In an investigation, it was estimated that the global prevalence of ADHD was 5.29% [131]. However, high prevalence percentages appear in some studies. Dealing with developmental pathologies, morbidly prevalent figures, which are far above 5%, require a cautious interpretation [124, 132]. Currently, the diagnosis is established by means of compliance with specific clinical criteria. These criteria are established in the two international scientific classifications: Diagnostic Criteria according to DSM IV TR and Diagnostic Criteria according to ICD-10 [124].

All this explains the importance of finding a biomarker (e.g. genetic tests, biochemical analysis, neurological explorations…) that can determine if a patient has ADHD or not. However, there are some neurological tests to help with the diagnosis, but they are merely complementary [133].

3. METHODOLOGY

3.1. Study design and participants

A total of 53 adults were selected for this prospective study. The control group was formed by 22 subjects (12 women); and the other group consisted of 31 adults with combined ADHD (16 women). The participants from the ADHD group were selected by the Vall d'Hebron Hospital in Barcelona (Spain), by a group of psychiatrists and psychologists that ensure that all of them sufficed the DSM-IV criteria [134] for ADHD combined subtype and were medication naïve. Moreover, exclusion criteria included comorbidity personality disorders or other psychiatric diseases, substance abuse disorder (including the ones that have consumed either tobacco or cannabis within the 6 months previous to the image acquisition) and an IQ lower than 80.

TABLE II
DEMOGRAPHIC DATA

	ADHD (*n = 31*)	Control (*n = 22*)	T / X^2	*p*
Age	34.742 ± 9.044	30.318 ± 5.735	-2.176	0.019
Gender	12/10	16/15	1.756	0.203
FD	0.054 ± 0.036	0.036 ± 0.030	-1.976	0.028
Coil	16/6	17/14	0.043	0.852
ADHD-RS				
Combined	32.323 ± 9.782	-	-	-

Table 2: Clinical demographic characteristics of the sample.

3.2. MRI acquisition and image processing

In order to acquire the images in this study, a Philips Achieva 3T Scanner was used. Statistically speaking, group was independent from gender (χ^2 = 0.043; p = 0.852)

therefore it was not included as a covariate. Due to technical problems, 20 of the participants were acquired using a different radiofrequency (RF) head coil, but they were homogeneously distributed across groups (χ^2 = 1,756; p = 0.203). The sequence used to obtain the T1-Weighted images was a fast spoiled gradient echo (FSPGR) with a repetition time (RT) of 8.2 ms, an echo time (ET) of 3.7 ms, a flip angle (FA) of 88º and a matrix with dimensions of 256x256x180, with a voxel size of 0.94x0.94x1 mm and no gaps. Moreover, to obtain the whole volumes at once, an echo-planar imaging (EPI)-T2* sequence with 116 time points each lasting 2.655 s was run. The parameters of that sequence were an in-plane 1 mm-gapped matrix with dimensions of 128x128 and a voxel size of 1.80x1.80 mm, with a slice thickness of 3.0 mm and an ET, RT and FA of 35 ms, 3000 ms and 90º, respectively. During the acquisition, patients were asked to remain both awake and still with open eyes.

After the acquisition process, the fMRI data was pre-processed with SPM12 in order to remove as much noise as possible. First step consisted of removing the first volumes (in our case 3) since they are mainly contributions of the magnetic field aligning proton molecules in the head, resulting in non-useful data for the study. Then, for motion correction images were realigned to the mean image and with the use of 3D Despiking AFNI tool, signal outliers were removed. Moreover, to compare the different images from each subject, they were normalized to Montreal Neurological Institute (MNI) standard space and to increase the signal-to-noise ratio they were spatially smoothed by the use of a Gaussian kernel with a full-width-half-maximum (FWHM) of 6mm. Finally, our images were down-sampled to 4 mm voxel size and nuisance variables were regressed out to remove undesirable effects.

3.3. Local and distant FC analysis

The local and distant FC technique is a measure of how much a voxel is functionally connected within its neighborhood and with distant parts of the brain, respectively [135]. Briefly, for each subject we first obtained a connectivity matrix, which contains the pairwise functional connectivity of all voxels. That is, therefore an N x N matrix (being

N the number of voxels) containing the Correlation Coefficient of the time series of each pair of voxels. Then we binarized the matrix by substituting values higher than 0.25 with one and the rest set to 0 (as it was described in the original work of J. Sepulcre [135]). Then, the degree of local and distant functional connectivity was computed. We defined as local connectivity the cube of 7x7x7 voxels (21952 mm^3) surrounding each voxel, and we calculate local connectivity values as the degree centrality (i.e. measure used to quantify the number of either edges or links that are connected to a node) of each voxel within its cube. For the distant connectivity maps we computed the degree centrality of each voxel with respect to outside their neighborhood.

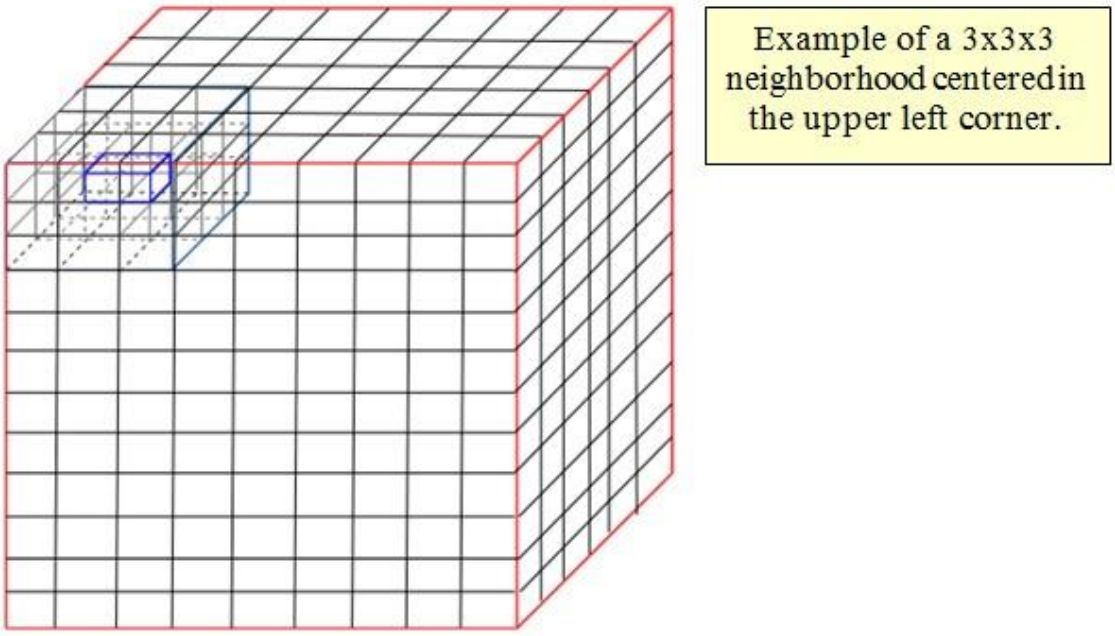

Figure 9: Local connectivity cube representation. Example ofa3x3x3voxels (1728 mm^3) surrounding a voxel that will be used to define local connectivity value.

Functional connectivity values were then corrected for voxel position. When computing local connectivity in a voxel whose neighborhood falls completely within the brain, it will have higher probability of sharing more links, therefore resulting in a more potential local connectivity than voxels lying in the border of the brain, which is also translated in less potential distant connectivity.

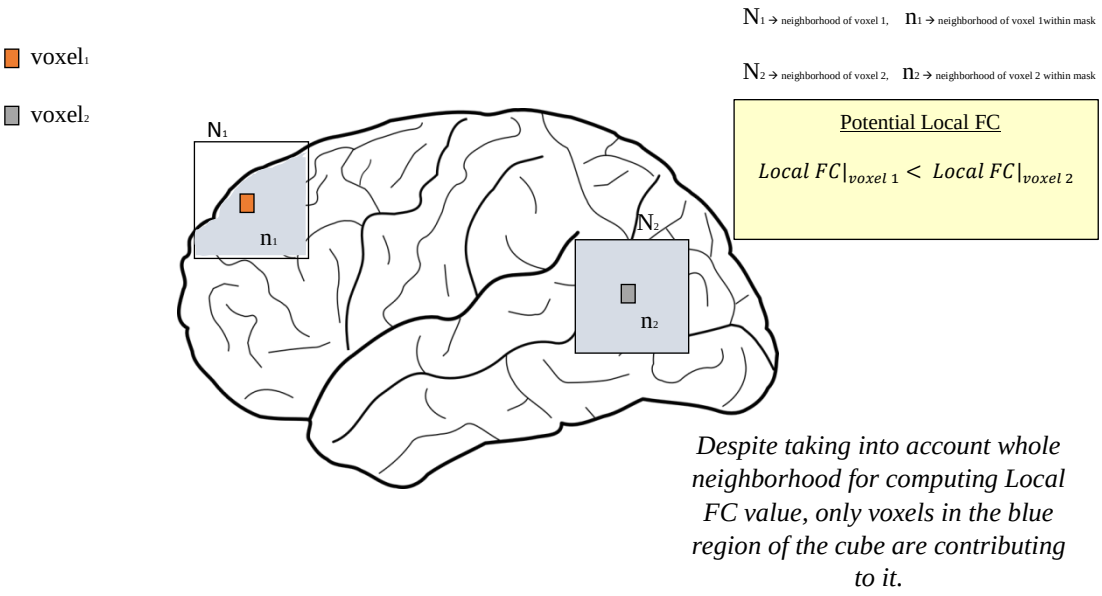

Figure 10: Visual explanation of why functional connectivity map value correction is required. As it can be seen, while whole neighborhood of voxel 2 is within the mask and contributed to the local FC value, part of the neighborhood of voxel 1 is outside the mask, therefore not contributing to local FC. If whole region instead only the neighborhood within the mask were taken into account, less potential local FC would be obtained.

The corrected local functional connectivity value $\widehat{l_i}$ was obtained by:

$$\widehat{l_i} = \frac{l_i}{L_i}$$

l_i is the local functional connectivity value of the i^{th} voxel and L_i the number of voxels within the i^{th} voxel's cube that fall inside the mask. $\widehat{l_i}$ will range between 0 and 1.

With respect to the corrected distant functional connectivity value $\widehat{d_i}$, it was computed by:

$$\widehat{d_i} = \frac{d_i}{n - L_i}$$

Where d_i is the distant functional connectivity value of the i^{th} voxel, n is the total number of voxels within the mask (constant) and L_i the number of voxels within the i^{th} voxel's cube that fall inside the mask. $\widehat{d_i}$ also will go from 0 to 1.

3.4. Statistical analysis

To evaluate the connectivity patterns in adults with and without ADHD, we transformed the group mean local and distant functional connectivity maps to Z-score maps. With this transformation the maps have mean equal to 0 and a standard deviation equal to 1, which means that each value represents the number of standard deviations above or beneath the mean. Thus, for each map the mean and the standard deviation (std) are first computed and then Z-scores are obtained.

$$\text{Given } N = \begin{pmatrix} n_1 \\ n_2 \\ \vdots \\ n_n \end{pmatrix},$$

$$mean\ (\bar{N}) = \frac{(\sum_{i=1}^{n} n_i)}{n}$$

$$variance\ (\hat{s}^2) = \frac{(\sum_{i=0}^{n}(n_i - \bar{N})^2)}{n-1}$$

$$std\ (\hat{s}) = \sqrt{\frac{(\sum_{i=0}^{n}(n_i - \bar{N})^2)}{n-1}}$$

$$Z_i = \frac{n_i - \bar{N}}{\hat{s}}$$

As stated, Z-score values were only used for visualization purposes and all subsequent analyses were performed using the local and distant connectivity values.

3.4.1. Linear models

To compare the local and distant functional connectivity maps between adults with ADHD and the control sample two General Linear Models were fitted in SPM12, one that explains the local and the other one the distant functional connectivity values. In each of them group, age, motion and head coil were included as regressors, being all except group and coil centered to the mean. To see whether there is a relationship between local and distant functional connectivity values and clinical symptoms, a regression analysis was performed only with the ADHD group. The analysis was performed using SPM12 and

described by two General Lineal Models with local and distant functional connectivity as dependent variables and age, motion, ADHD score and coil as independent variables, being the first three centered to the mean.

3.4.2. Multiple comparison correction

Once the models were fitted, specific contrasts were defined for testing group differences and the relationship with ADHD clinical symptoms. Then, we obtained statistical maps that were thresholded with $p < 0.005$ and a cluster size (K) of at least 12 contiguous voxels, which corresponds to a cluster-wise Family Wise Error (FWE) corrected p-value of 0.01 ($p^{FWE} < 0.01$). The FWE correction was estimated with the AFNI program 3dClustSim [136] (accessed September 11, 2018), which performs a Montecarlo simulation based on the image size, the search volume and the spatial correlation of the image [137].

3.4.3. Visualization

Results were interpreted in terms of brain networks by computing the percentage of voxels pertaining to each of the seven cortical and subcortical large-scale resting state functional networks described by Yeo et al.(2011) [138] and plotted in a pie chart.

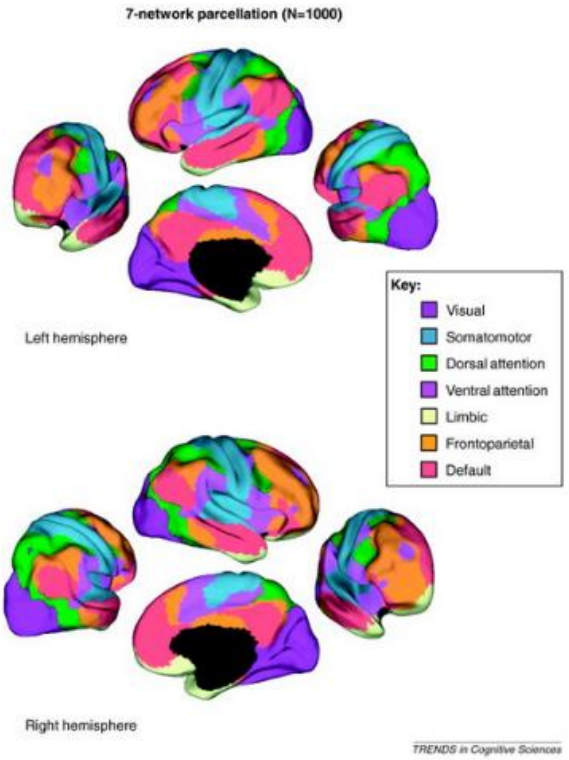

Figure 11: large scale resting state functional networks described by Yeo et al. [138]

Percentages were computed over the total amount of significant voxels surviving the threshold of $p^{FWE} < 0.01$ and the pie charts were performed by an in-house Matlab script. Moreover, regression plots were performed for clinical symptoms analysis. The plots were performed by also an in-house Matlab script. In it, normalized functional connectivity vs ADHD scores were plotted together with the correlation coefficient (r), which is given by:

$$r = \frac{t}{\sqrt{DF + t^2}}$$

$$where\ DF = n - k - 1\ with \qquad \begin{matrix} n = number\ of\ subjects \\ k = number\ of\ indep. variables \end{matrix}$$

3.5. Image packages

In order to perform the statistical analysis and the visualization of the results three main packages were used, SPM12, Connectome Workbench and MricroGL.

3.5.1. SPM12

Statistical Parametric Mapping (SPM12) it is a free open-source package that needs MATLAB to be run. It was developed by *Karl Friston* and his colleagues at the University College London in the Functional Imaging Laboratory [139], with the aim of providing a tool for brain imaging data sequences' analysis, such as images from different cohorts. Because it is designed for multiple modalities such as EEG or PET, once opened in MATLAB, fMRI must be selected. Then the statistical functions section will be used to specify, review and estimate analyses. After this, the results option will be used to load the SPM.mat file and be directed to the contrast manager. Then, a threshold is introduced. SPM allows you to restrict even more the results by defining the minimum size of the clusters of voxels (K). Both the threshold and the cluster size were obtained through Montecarlo simulation. Finally, the results will be visualized. SPM gives you as output a glass brain with the activation map and a table containing all clusters that survived to the chosen level of significance as well as separate more than 8 mm apart maxima within a cluster [140].

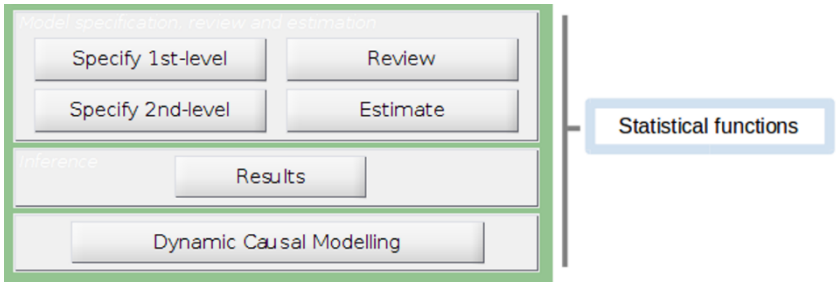

Figure 12: Main menu section with the statistical functions offered by SPM.

3.5.2. Connectome Workbench

Connectome Workbench is a free open-source tool used for visualization and discovery. In it, neuroimaging data is mapped. It includes a command-line program (wb_command) for performing tasks using for example volumes or surfaces, and wb_view, which is the GUI-based visualization platform [141]. Surface templates were obtained from Connectome DB https://db.humanconnectome.org/app/template/Login.vm, specifically from the Human Connectome Project (HCP). Such surfaces are geometric files (*surf.gii) that through triangular tiling define 3D vertex coordinates and their topological relationships. The main templates we focused on are pial and inflated surfaces. By default SPM12 give NifTi files (*.nii) which are of type volume format. In order to visualize them we need their conversion into metric files (*func.gii or *shape.gii). This is done by using volume-to-surface wb_command operator [142]. Then we open the files and map them onto the surface templates with the use of the overlay Toolbox. In order to be able to compare obtained results, data was previously normalized and palette of the mapped metric files are changed in *Overlay and Map settings* option.

3.5.3. MricroGL

MricroGL is a free open-source program used for displaying 3D medical images. Software is obtained from https://www.nitrc.org/frs/?group_id=889. While Connectome Workbench is used for main visualization, there are some clusters that are not on the surface but inside the brain. In order to visualize them, this tool is used by simply overlaying the thresholded SPM .nii files.

4. RESULTS

4.1. Group characterization

Figure 13 displays the local and distant functional connectivity Z-score maps for both control and ADHD samples. For comparison purposes, functional connectivity maps of normal developing (ND) and ADHD children calculated by Marcos-Vidal L. et al [14] were included.

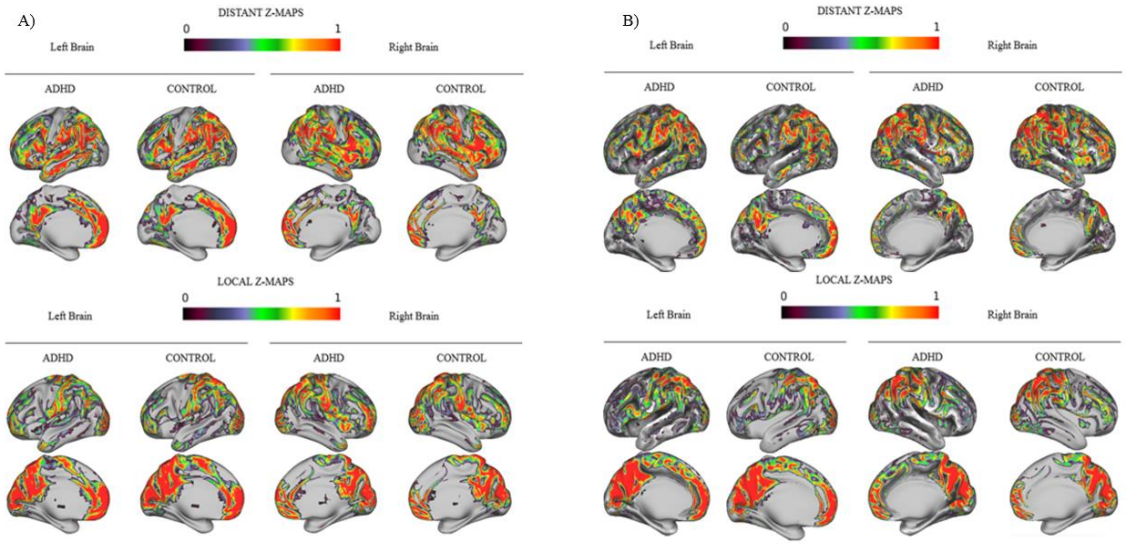

Figure 13: Lateral and medial views of both left and right hemispheres are shown. In A) ND and ADHD children distant and local FC maps and B) control and ADHD adults FC maps. The color bar represents normalized Z-scores, where 0 corresponds with that Z-score value and 1 corresponds with a Z-score value equal or greater than 1 [14].

4.2. Between groups comparison

Figure 14 and table III show the results of the 2-sample T-test after thresholding with $p < 0.005$ and $K = 12$ ($p^{FWE} < 0.01$). Adults with ADHD exhibited a decreased degree of local FC in Frontal Gyrus, Precuneus and Right Superior Parietal Lobule (Table II and Figure 14a). In terms of functional networks, as it is shown in Figure 14b, these areas pertain mainly to the DMN. However, other networks such as the FP, Visual and DA are also involved. With respect to distant FC, no cluster survived after restricting the results neither for CTRL>ADHD nor ADHD>CTRL contrasts.

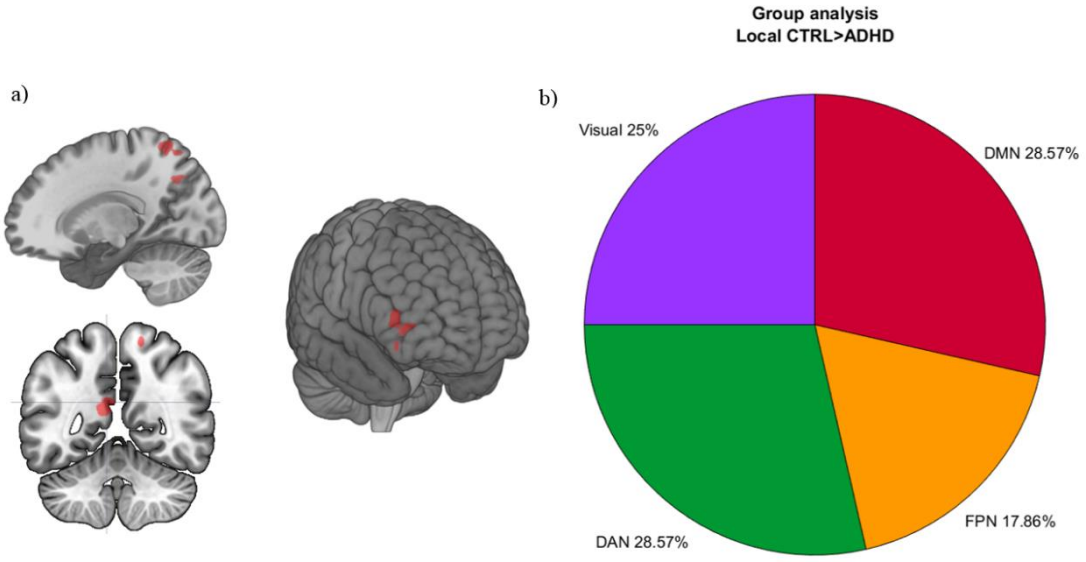

Figure 14: a) Coronal, sagittal and whole brain views shown in red altered local FC regions that survived after multiple comparison correction, b) Pie chart representation of altered regions in terms of networks. Percentages were obtained based only on affected anatomical areas.

TABLE III
BETWEEN GROUP FUNCTIONAL CONNECTIVITY

	Cluster size (mm^3)	x(mm)	y(mm)	z(mm)	Network	T	p-value
LOCAL CONNECTIVITY							
CTRL>ADHD							
Frontal Gyrus	1088	52	40	8	FP	5.07	<0.001
		52	48	0	FP	3.31	0.001
		52	43	-8	Default	2.87	0.003
Right Precuneus	1024	12	-66	36	Default	4.05	<0.001
Right Occipital Gyrus		24	-86	41	Default	3.32	0.001
Precuneus		4	-62	36	Visual	3.24	0.001
Left Precuneus	1536	-12	-51	19	Default	3.86	<0.001
		-8	-59	23	Dorsal	3.78	<0.001
Right Superior Parietal Lobule	1280	16	-56	63	Dorsal	3.83	<0.001
		12	-65	60	Visual	3.57	<0.001
ADHD>CTRL							
None							

Table 3: Between group functional connectivity view. Coordinates are based on MNI152 stereotactic space. Results reported in the table correspond to those clusters above 768 mm^3 (12 contiguous voxels).

4.3. Clinical correlations

Figure 15a and table IV shows the results of the regression analysis after thresholding with $p<0.005$ and $k=12$. We found several regions whose local functional connectivity was negatively correlated with ADHD clinical symptoms. Concretely, the lower the local Connectivity in the Precuneus and Posterior Cingulate Cortex, the higher the ADHD score. In terms of functional networks, although the visual network is involved, the regions again correspond mainly to the DMN, as represented in Figure 15b. Figure 16 displays the significant clusters on brain's surface and the regressions.

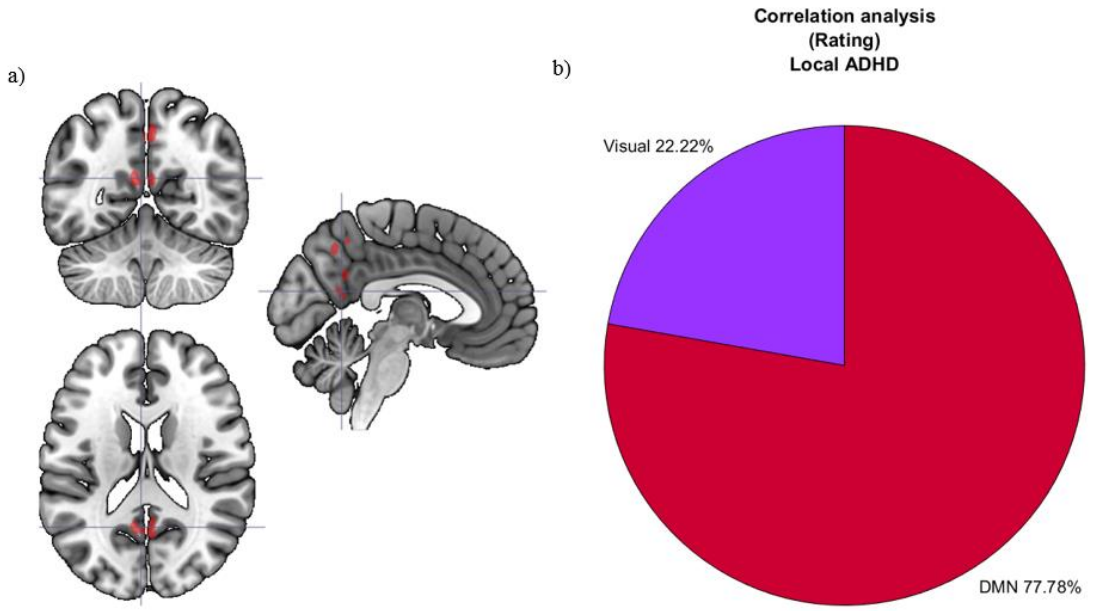

Figure 15: a) Coronal, sagittal and axial brain views shown in red altered local FC regions that survived after multiple comparison correction, b) Pie chart representation of altered regions in terms of networks. Percentages were obtained based only on affected anatomical areas.

TABLE IV
RATING CORRELATION ANALYSIS

	Cluster size (mm^3)	x(mm)	y(mm)	z(mm)	T	R^2	p-value
LOCAL CONNECTIVITY							
ADHD(-)							
Left Precuneus/Left Posterior Cingulate Gyrus	1088	-8	-55	19	4.12	0.40	<0.001
Precuneus		4	-63	20	3.16	0.28	0.002
Precuneus/Right Posterior Cingulate Gyrus		-4	-55	27	2.93	0.25	0.003
Precuneus	1408	4	-53	51	3.83	0.36	<0.001
Precuneus		4	-62	44	3.76	0. 35	<0.001
ADHD(+)							
None							

Table 4: Rating correlation analysis table view. Coordinates are based on MNI152 stereotactic space. Results reported in the table correspond to those clusters above 768 mm^3 (12 contiguous voxels). Clinical severity score was based on the ADHD Rating Scale (ADHD-RS).

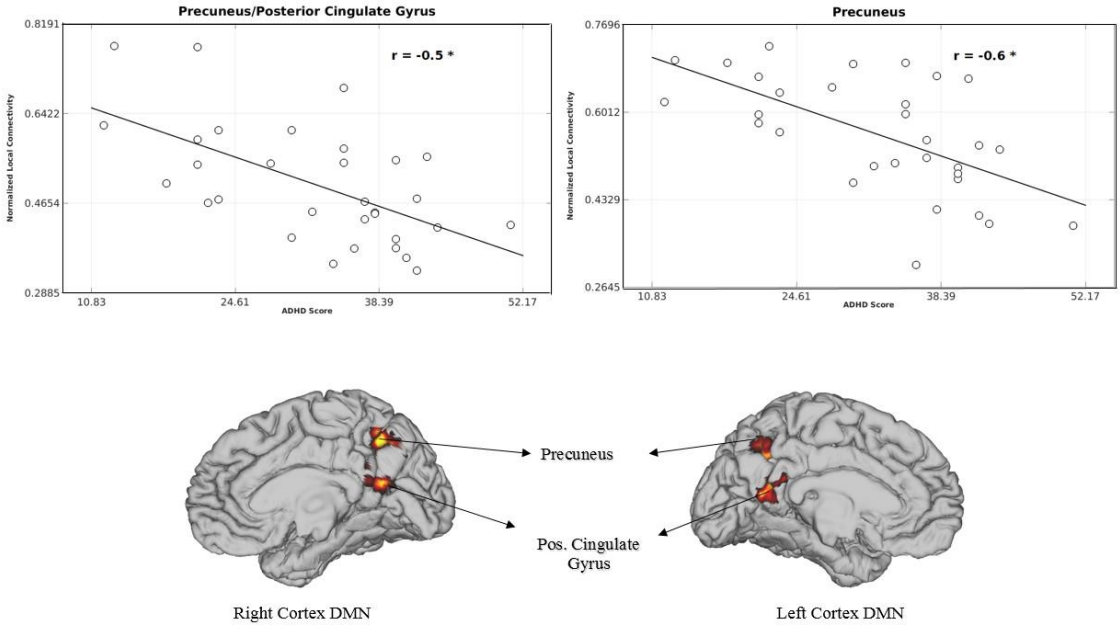

Figure 16: In a) Graphs are showing relationship of ADHD local connectivity and clinical symptoms. In b) medial views of the left and right hemisphere show regions whose local connectivity is negatively related to ADHD scores.

5. DISCUSSION

This study cross-sectionally compared the local and distant functional connectivity patterns between adults with ADHD and controls. We found that adults with ADHD reported decreased local functional connectivity in multiple brain networks while distant functional connectivity was preserved. Our results are in line with those found in children, pointing out to ADHD as a disorder of deviated trajectories where multiple brain networks shared an immature functional state [14]. However, these delayed patterns of functional connectivity do not seem to completely "catch up" neither through adolescence nor after reaching adulthood, which follows the hypothesis of abnormal development.

Initially, multiple neurocognitive hypotheses regarding ADHD focused on alterations within a specific brain location [81], but nowadays, neurobiological models suggest alterations at the level of multiple functional networks [81, 103]. Roughly speaking, increased integration within sensory networks and decreased segregation between multiple networks support the idea of an alteration of brain trajectories in ADHD. Results suggest that the decreased functional connectivity found in several functional networks of the ADHD group reflects a lack of integration and thus, an immature state of those networks.

Within the pattern of local functional connectivity in ADHD, the affected areas include the Precuneus, Frontal Gyrus, Right occipital Gyrus and Right Superior Parietal Lobule. Functionally, these regions belong mainly to the DM, FP, visual and DA networks respectively. In the area of the Precuneus mainly a lack of integration is observed. In a study of Fair DA.et al, 2010, [14] decreased DMN integration in both adults and children with ADHD was found. In Castellanos FX et al, 2008 [115]; adults with ADHD showed abnormal connectivity patterns between the Precuneus and the medial prefrontal cortex, which are key nodes of the DMN, respectively. While these results point to a lack of integration between different nodes of the DMN, ours suggest that the integration is compromised even within the Precuneus node.

Additionally, a cross-sectional study reported results consistent with a lag of FC maturation in terms of DMN integration and FP and DM networks segregation [7] and,

moreover, the lack of segregation in such networks results in attentional lapses [11]. In 2007, Castellanos and Sonuga-Barke [144] proposed the default-mode interference hypothesis in which they stated that under certain circumstances the DMN re-activate during task-performance competing with task-specific neural processing creating the context of the already mentioned attentional lapses. Since we also found a lack of integration in the FPN by the decreased local connectivity in the frontal gyrus, it would be interesting to assess whether this lack of integration within nodes of DMN and FPN is related with the lack of segregation between them.

Abnormal local connectivity patterns were also found in the right superior parietal lobule, a region that pertains mainly to the DAN. Aberrant connectivity within the dorsal attentional network as well as the interplay between dorsal attentional and DMN [16] has been previously observed in ADHD. Moreover, decreased segregation between the DMN and DAN [10, 145] was reported. Interestingly, it was found that altered functional connectivity between the Posterior cingulate and the Dorsal Anterior Cingulate cortices appear to be more similar to the connectivity pattern found in typically developing children than healthy control adults suggesting a potential delay in maturation in ADHD [145].

Within the visual network, the reduction of local functional connectivity suggests less integration in the visual cortex of adults with ADHD, as supported by Gülsüm Akdeniz, 2017 [146]; while the opposite is observed in children with ADHD [147, 14].

It is necessary to mention that after pertinent corrections the deficits observed in the regions belonging to FP, DA, visual and DM networks do not imply that the alterations are limited to these functional networks. Indeed, we propose that our results should be understood in the context of a more global state of deviant maturation affecting the whole brain as altered brain network's function is the basis of altered brain functioning [148].

With respect to clinical correlations, we found that clusters in regions belonging to both the visual and mainly the DM networks shared a negative correlation between local functional connectivity and ADHD symptoms. It has already been shown that in fact the lack of attention is correlated with alterations in connectivity within the DM network [149]. Results suggest a negative correlation between symptom severity and local functional connectivity. That is, the more severe symptoms are, the lesser local functional

connectivity within the Precuneus and the Left Posterior Cingulate Gyrus, which are key hubs of the DMN and reinforce the idea of reduced integration within such network.

The present study has some limitations. The first one is that functional connectivity analyses are only focused on cortical regions. Despite the fact that most of the areas altered in ADHD belong to such regions, the cerebellum which indeed has been shown to be involved in ADHD is not included, and therefore it is not analyzed. Another main limitation is the sample size. Too small sample sizes reduce the reliability of the results, because it reduces statistical power and increases the effect of outliers among others [150]. Finally, the use of cross-sectional data for inferring developmental trajectories is also considered as an important drawback. Even though often used in the investigation of developmental processes, achieved conclusions are weaker than in longitudinal studies [151].

We have shown the atypical local and distant functional connectivity patterns in adults with ADHD with respect to controls. Results were consistent with decreased local functional connectivity in DM, FP, DA and visual networks, that is; reduced integration within nodes of that networks. Moreover, a negative correlation between symptom severity and functional connectivity has been found within main nodes of DMN supporting that the lack of integration is directly related to symptom severity. Subsequent longitudinal connectivity studies with large sample sizes should be conducted not only to enable better understanding of differences between ADHD children and adults but also to contribute to the identification of the abnormal developmental principles that arise behind the apparent maturational lag that does not catch up with time.

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